$[Ag(CH_2Cl_2)_2]_2[Pd(OTeF_5)_4]$ (2.775 (2)–2.882 (2) Å).[10]

The most significant feature of the structure is the absence of Ag–O bonds, which are present in $[Ag(CH_2Cl_2)_2]_2[Pd(OTeF_5)_4]$,[10] $AgB(OTeF_5)_4$,[11b] and $[Ag(CO)][B(OTeF_5)_4]$.[11d] Instead, each $[Ag(CH_2Cl_2)_3]^+$ cation is only *extremely weakly coordinated* to the $Ti(OTeF_5)_6^{2-}$ anion by two Ag···F contacts of 3.029 (8) and 3.033 (6) Å. For comparison, the Ag–F distances in $AgSbF_6$[20] and AgF[21] are 2.62 and 2.467 (3) Å, respectively, and the sum of the van der Waals radii for silver and fluorine is 3.15 ± 0.08 Å.[22] The relative strength of anion binding to Ag^+ is also evident in the number of dichloromethane molecules coordinated to Ag^+—three in $[Ag(CH_2Cl_2)_3]_2[Ti(OTeF_5)_6]$ but only two in $[Ag(CH_2Cl_2)_2]_2[Pd(OTeF_5)_4]$.

In contrast with the $B(OTeF_5)_4^-$ anion,[11b] $Nb(OTeF_5)_6^-$ does not undergo rapid exchange with labeled $OTeF_5^-$ in the presence of electrophilic cations such as H^+ and Ag^+. For example, when $[TBA][Nb(^{16}OTeF_5)_6]$ and $H^{18}OTeF_5$ were mixed in dichloromethane at 22 °C, IR spectra showed that isotope scrambling was only 22% complete after 47 h. The presence of a larger cation had an even more dramatic effect: when $AgNb(^{16}OTeF_5)_6$ and $Ag^{18}OTeF_5$ were mixed in dichloromethane at 22 °C, *no* exchange was observed after 72 h. On the basis of the structure of $[Ag(CH_2Cl_2)_3]_2[Ti(OTeF_5)_6]$, we propose that electrophiles larger than H^+ cannot form bridge bonds to the *oxygen* atoms of $Nb(OTeF_5)_6^-$. Without such bridge bonds, abstraction of $OTeF_5^-$ by even the strongest electrophiles will not occur rapidly. Thus, steric hindrance causes a *kinetic* stabilization of $Nb(OTeF_5)_6^-$ (and presumably of other structurally related anions as well) in the presence of electrophilic cations.

Our new silver salts are freely soluble in weakly coordinating, low dielectric solvents such as chlorinated hydrocarbons and chlorofluorocarbons. For example, the solubility of $Ag_2Pd(OTeF_5)_4$ in dichloromethane at 22 °C ($\epsilon \approx 9.1$) is only 0.35 M,[10] while the solubility of $Ag_2Ti(OTeF_5)_6$ is *many* times higher (in fact, its solubility is sufficiently high that measuring it quantitatively has been problematic). An even more striking example of solubilizing ability is evident when comparing solubilities in CFC-113 at 22 °C ($\epsilon \approx 2.4$): $AgOTeF_5$, insoluble; $AgB(OTeF_5)_4$, 0.004 M; $AgNb(OTeF_5)_6$, 0.4 M.

The anions $Nb(OTeF_5)_6^-$ and $Ti(OTeF_5)_6^{2-}$ have the potential of being less coordinating, more stable in the presence of electrophilic cations, and more solubilizing than any previously reported anions. Detailed comparisons with anions such as $B(3,5\text{-}C_6H_3(CF_3)_2)_4^-$ and $CB_{11}H_{12}^-$ will be reported in a full article. The use of $Nb(OTeF_5)_6^-$, $Ti(OTeF_5)_6^{2-}$, and other very large, highly fluorinated anions for the preparation, isolation, and complete characterization of "coordinatively unsaturated" metal and metalloid cations remains an active endeavor in this laboratory.

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Supplementary Material Available: Tables S-I–VI, listing crystallographic data, atomic coordinates and isotropic thermal parameters, bond distances, bond angles, anisotropic thermal parameters, and hydrogen atom coordinates and thermal parameters (8 pages); Table S-VII, listing observed and calculated structure factors (10 pages). Ordering information is given on any current masthead page.

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A General and Expedient Method for the Solid-Phase Synthesis of 1,4-Benzodiazepine Derivatives

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Very powerful methods have recently been developed for the combinatorial synthesis of large libraries of peptides which are then screened against a specific receptor or enzyme in order to determine the optimal peptide sequence for high affinity to that receptor or enzyme.[1] Unfortunately, peptides have limited utility as bioavailable therapeutic agents because they generally cannot be taken orally and have rapid physiological clearing times. The combinatorial synthesis and screening of bioavailable organic compounds would be a powerful extension of this approach. In this communication we report a general method for the expedient solid-phase synthesis of 1,4-benzodiazepine derivatives,[2] the critical first step in the combinatorial synthesis and screening of one of the most important classes of bioavailable therapeutic agents.[3] Because benzodiazepines are not polymers like the peptides and oligonucleotides that have previously been synthesized on solid support,[4] this report also demonstrates an important extension of solid-phase synthetic methods from the synthesis of biopolymers to the synthesis of nonpolymeric organic compounds.[5]

The 1,4-benzodiazepine derivatives are constructed on solid support from three separate components: 2-aminobenzophenones, amino acids, and alkylating agents (Scheme I). The 2-aminobenzophenone derivatives **1** are first attached to the polystyrene solid support through either a hydroxy or carboxylic acid functionality employing the acid-cleavable linker [4-(hydroxymethyl)phenoxy]acetic acid.[6] Synthesis of the benzodiazepine derivative on solid support then proceeds by removal of the FMOC protecting group from **2** by treatment with piperidine in DMF followed by coupling the resulting unprotected 2-aminobenzophenone to an α-*N*-FMOC-amino acid (Scheme I). Amide bond formation does not occur when the standard activation methods employed in solid-phase peptide synthesis are used (for example, carbodiimides and hydroxybenzotriazole or pentafluorophenyl active esters); however, treatment of the 2-aminobenzophenone with a methylene chloride solution of the α-*N*-FMOC-amino acid fluoride[7] in the presence of the acid scavenger 4-methyl-2,6-di-*tert*-butylpyridine results in complete coupling to provide amide **3**. The coupling conditions are suitable even for unreactive aminobenzophenone derivatives since complete coupling is observed for a derivative of **2** which contains both the *p*-chloro and the *m*-carboxy deactivating substituents (see **6i** and **6j** in Table I).

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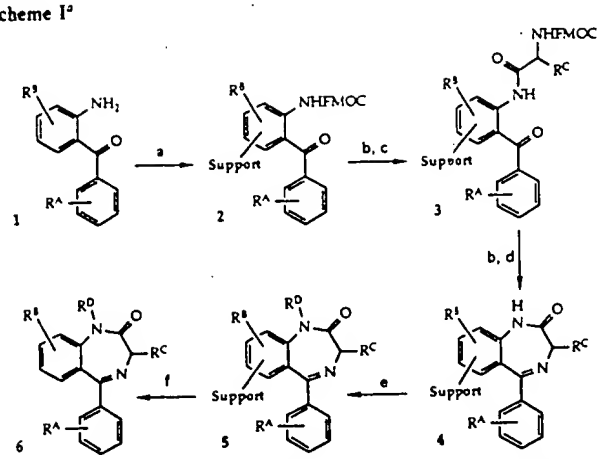
Scheme I[a]



[a] (a) See supplementary material; (b) 20% piperidine in DMF; (c) *N*-FMOC-amino acid fluoride, 4-methyl-2,6-di-*tert*-butylpyridine; (d) 5% acetic acid in DMF, 60 °C; (e) lithiated 5-(phenylmethyl)-2-oxazolidinone in THF, −78 °C, followed by alkylating agent and DMF; (f) TFA/H_2O/Me_2S (95:5:10).

Table I. 1,4-Benzodiazepine Derivatives 6 (Scheme I)

entry	derivative R^A	R^B	R^C	R^D	yield (%)[a]
6a	4'-OH	5-Cl	CH_3	H	95
6b	4'-OH	5-Cl	CH_3	CH_3	100
6c	4'-OH	5-Cl	CH_3	CH_2CH_3	97
6d	4'-OH	5-Cl	CH_3	CH_2CHCH_2	90
6e	4'-OH	5-Cl	$CH(CH_3)_2$	CH_2CH_3	85
6f	4'-OH	5-Cl	CH_2CO_2H	CH_2CH_3	95
6g	4'-OH	5-Cl	$(CH_2)_4NH_2$	CH_2CH_3	95
6h	4'-OH	5-Cl	$CH_2Ph(4\text{-}OH)$	CH_2CH_3	98
6i		4-CO_2H,5-Cl	CH_2Ph	CH_3	100
6j		4-CO_2H,5-Cl	CH_3	CH_2Ph	93

[a] Yields are based on support-bound starting material 2.

The FMOC protecting group in 3 is then removed by treatment with piperidine in DMF. Exposure of the resulting free amine to 5% acetic acid in DMF provides the cyclic product 4. Complete cyclization is observed in the synthesis of 1,4-benzodiazepine derivatives with various steric and electronic properties (Table I), again demonstrating that general conditions have been identified for the solid-phase synthesis of diverse benzodiazepine derivatives.

Alkylation of the anilide of 4 then provides the fully derivatized 1,4-benzodiazepine 5 (Scheme I). Ideally, an excess of the base would be employed to achieve complete deprotonation and alkylation of the anilide, but employment of excess of commonly used bases such as LDA or NaH would result in deprotonation and subsequent alkylation of acidic functionality present elsewhere in the molecule. To maximize synthesis generality we therefore chose to employ lithiated 5-(phenylmethyl)-2-oxazolidinone[8] as the base since it is basic enough to completely deprotonate the anilide of 4, but not basic enough to deprotonate amide, carbamate, or ester functionalities. Upon deprotonation of 4, the appropriate alkylating agent is added followed by addition of anhydrous DMF to accelerate the alkylation reaction. By employing these conditions 1,4-benzodiazepine derivatives containing esters and carbamates have been alkylated in high yields on solid support with no overalkylation observed (compounds 6f and 6g in Table I where side chains were protected as a *tert*-butyl ester and a *tert*-butyl carbamate, respectively). Complete alkylation is observed for both activated alkylating agents such as methyl iodide and benzyl bromide and unactivated alkylating agents such as ethyl iodide.

The benzodiazepine product 5 is cleaved from the support with concomitant removal of acid-labile protecting groups by exposure to 85:5:10 trifluoroacetic acid/water/dimethyl sulfide. Employing this reaction sequence we have synthesized multiple structurally diverse benzodiazepine derivatives 6 in very high overall yields (Table I). In addition, racemization does not occur during the reaction sequence as determined by chiral HPLC analysis of the benzodiazepine derivatives 6a and 6c prepared from both (*R*)- and (*S*)-*N*-FMOC-alanine (Table I).[9] With the employment of this general and expedient solid-phase synthesis methodology, the construction and screening of a large combinatorial library of benzodiazepine derivatives are currently in progress and will be reported shortly. The solid-phase synthesis of other classes of therapeutically important organic compounds is also under investigation and will be reported in due course.

Supplementary Material Available: Listings of experimental procedures for attaching the aminobenzophenone derivatives to the solid support and for the solid-phase synthesis of the benzodiazepine derivatives, including analytical data for all of the 1,4-benzodiazepine derivatives and intermediates (8 pages). Ordering information is given on any current masthead page.

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Direct Evidence for an Oxocarbenium Ion Intermediate in the Asymmetric Cleavage of Chiral Acetals

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The Lewis acid mediated cleavage of chiral acetals has been the subject of numerous investigations over the past several years and is a useful tool for the asymmetric synthesis of carbon–carbon bonds.[1] With allylsilanes[2] and allylstannanes[3] as nucleophiles, this reaction can provide chiral ethers with diastereoselectivities ranging from 5:1 to >500:1. The origin of this selectivity has been studied, mostly by studying the behavior of model acetals,[4] but these studies are inconclusive because the behavior of the model compounds is known to vary with minor variations in the structure of the acetals.[5] We wish to report the results of a more direct approach to studying the reactivity of chiral acetals which utilizes the stereospecifically deuterated acetal 1[6] (Table I) to determine

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